REMARKS

Claims 1-36 were previously pending in the present application. Claims 17-36 have been withdrawn. In this response, claims 1, 3-4, 9-13, 16 have been amended and claims 37-39 have been added. The amendments to the claims and the new claims are supported by the specification as filed, and as such do not add new matter. The following chart provides exemplary support for each of these claims in the specification as published.

Claims	Support in Specification
1	Originally filed claim 1, Figures 2-4 and paragraphs [0016], [0073], [0075], [0076] and [0077]
3	Originally filed claim 3
4	Originally filed claim 4, Paragraph [0068], Example 5
9	Originally filed claim 9, paragraph [0068], Example 5
10	Originally filed claim 10
11	Originally filed claim 11
12	Originally filed claim 12
16	Originally filed claim 16
37, 38, 39	Originally filed claim 1, Figures 2-4 and paragraphs [0016], [0073], [0075], [0076] and [0077]

Priority

The Office Action states that the declaration filed April 2, 2004 does not state that Applicants claim priority to any earlier application, while the specification states that the present application claims priority to Chinese Patent Application No. 01126278.8, filed July 19, 2001. The Office Action requests clarification in this regard.

Applicants confirm that the statement regarding priority in the April 2, 2004 declaration is an inadvertent error. As correctly set forth in the specification as originally filed, the present application claims priority to Chinese Patent Application No. 01126278.8, filed July 19, 2001.

Specification and claim objections

The Office Action objects to paragraphs [0025] and [0026] for failing to set forth sequence identifiers for the amino acid sequences of Figures 2 and 3. Applicants have amended paragraphs [0025] and [0026] to specify that fragments (1), (2), (3), (4), (1'), (2'), (3'), and (4') correspond to SEQ ID NOs: 19-26, respectively.

The Office Action objects to the abbreviation "MWCO" in paragraph [0129], and requires that the abbreviation be spelled out in its first instance of use. Since the term "MWCO" appears first in paragraph [0127], applicants have amended paragraph [0127] to specify that "MWCO" refers to molecular weight cut-off.

The Office Action has suggested certain changes to claims 1, 3 and 16. Pursuant to such suggestions, "combination genes" in item (b) of claim 1 has been changed to "a combination of genes"; "expressing into" in item (e) of claim 1 has been changed to "expressing in"; "Xhol I" in claim 3 has been changed to "Xho I"; "Clostrispan or Trypsin" in claim 16 has been changed to "clostripain or trypsin."

Applicants respectfully submit that the above amendments to the specification and claims are sufficient to overcome the objections stated in the Office Action.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-16 were rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claim 1 has been amended to change the phrase "may encode" to "encodes;" the phrase "wherein N is integer from 1 to 32" to "wherein N is integer from 2 to 32;" the phrase "vector N copies of …" to "expression vector comprising N copies of …;" the phrase "combination" to "combination of;" the phrase "a fusion protein" to "a protein;" and the phrase "cleaving the fusion protein" to "cleaving said protein of step (e)." Claim 1 has also been amended to further clarify the steps of the claimed methods.

Claims 9 and 10 have been amended to change the phrase "may express" to "expresses." Claims 11-12 have been amended to change the phrase "can express" to "expresses." Claims 9-12 have also been amended to change the phrase "a fusion protein containing N copies of a polypeptide" to "a protein containing N copies of the series-linked polypeptide."

Claim 16 has been amended to change the phrase "claim 1 wherein said protease" to "claim 1 wherein said protein is cleaved at step (f) by."

Applicants respectfully submit that these amendments to the claims overcome the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1-16 and objects to the specification based on the reference deposit with the "China Committee for Culture Collection of

Microorganism General Microbiological Culture Center" under accession number "CGMCC No. 0559." According to the Office Action, there is no indication in the specification as to the public availability of this deposited material.

The specification expressly states at paragraph [0074] that Deposit Number CGMCC No. 0599 was made in accordance with the Budapest Treaty. Applicant has submitted herewith a declaration by an attorney of record verifying that this deposit was made under the Budapest Treaty, and that this deposit will be available irrevocably and without restriction or condition to the public in the event a patent issues from the present application.

Rejections under 35 U.S.C. §102

Claims 1, 4-5, 9-10, 13 and 16 have been rejected as anticipated by Rasmussen et al. (WO 9517510). Applicants respectfully disagree.

For the purposes of expediting the prosecution, claim 1 has been amended to further specify that the gene encoding GLP-1(7-36) or GLP-1 analogs contains a first, second and third restriction endonuclease cleavage sites, wherein the second restriction endonuclease cleavage site is located in the region between the first and third restriction endonuclease cleavage sites, the gene is digested at the first and third endonuclease cleavage site; and the vector has the second and third restriction endonuclease cleavage sites and is digested at these two sites; then the digested gene is ligated with the digested vector, wherein the first restriction endonuclease site of the gene forms a hybrid site with the second restriction endonuclease site of the vector. Such hybrid site is not subject to cleavage by either the first or the second endonucleases. Therefore, after the target gene is ligated into the vector,

the first endonuclease cleavage site is eliminated, and the resulting vector has only the second and third endonuclease cleavage sites. The foregoing steps may be repeated to insert multiple copies of the gene encoding GLP-1(7-36) or GLP-1 analogs into the vector.

Figure 4 of the present application shows an example of the steps described above. In step 2 of Figure 4, the vector is cleaved at the BamH I and Hind III sites (the second and third endonuclease cleavage sites), the GLP-1 gene is cleaved at the Bgl II and Hind III sites (the first and third cleavage sites). The GLP-1 gene is inserted into the vector at the BamH I site and the Hind III site wherein the cleaved Bgl II site on the GLP-1 gene binds to the cleaved BamH I site on the vector. The newly formed Bgl II/BamH I hybrid site cannot be cleaved by either Bgl II or BamH I. Step 2 may be repeated until the desired number of copies of the GLP-1 gene is inserted into the vector.

The advantage of the method of the present invention is that the target gene can be inserted into the vector sequentially in only one orientation, making it easy to have multiple copies of the target gene inserted into the vector.

On the other hand, Rasmussen et al. disclosed a method wherein multiple copies of the target genes were made using PCR overlap extension, then inserted into the vector by ligation (see, for example, Example 1, page 9, lines 7-9 of Rasmussen et al., which states that "[a] cassette of four GLP-1(7-36) coding units was assembled from synthetic oligonucleotides by polymerase chain reaction (PCR) overlap extension. In two separate PCR reactions single stranded oligonucleotide templates were joined."). The restriction enzyme digestion by BamHI and XbaI was

done after the cassette of four GLP-1(7-36) coding units was assembled (see, page 10, lines 15-16 of Rasmussen et al., which states that "[t]he amplified PCR product was digested with restriction endonucleases BamHI and XbaI ..."). Therefore, Rasmussen et al. does not teach using hybrid restriction endonuclease sites to sequentially insert single copy gene fragments of GLP-1(7-36) or its analogs into a vector.

Comparing to the present invention, the PCR overlap extension method used in Rasmussen et al. is not very efficient for making constructs with multiple copies of the target genes. When a template containing repeat sequences of the target genes is used, the primers may bind with any one of the repeats and create a mixture of constructs with various copies and sequence length of the target genes. Lots of time and money have to be spent to screen the constructs to find the desired construct. The method becomes less and less efficient as the number of copies of the target genes on the construct increases. Rasmussen et al. disclosed a construct containing only 4 copies of the GLP-1(7-36) gene probably because constructs with higher copies would be very difficult to make using their method. Also, the peptide yield of the method disclosed in Rasmussen et al. was very low, e.g. the yield in example 7 of the reference was as low as 2.7%.

Therefore, the present invention provides a different and more effective method for producing GLP-1 polypeptides and analogs thereof than Rasmussen et al. Rasmussen et al. does not anticipate amended claim 1.

Since claims 4-5, 9-10, 13 and 16 are dependent from claim 1 and contain all limitations of claim 1, Rasmussen et al. does not anticipate claims 4-5, 9-10, 13 and 16 either. The applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-5, 9-10, 13 and 16 were rejected under 35 U.S.C. §103 as obvious over Rasmussen et al.

As stated above, Rasmussen et al. does not teach or suggest to a person skilled in the art the sequential insertion of copies of the gene encoding GLP-1 (7-36) or GLP-1 (7-36) analogs into the vector through restriction endonuclease cleavage and ligation of hybrid endonuclease cleavage sites. The method claimed in the present invention is much more efficient for making constructs with tandem repeats of the target genes than the PCR overlap extension method used in Rasmussen et al. Therefore, Rasmussen et al. does not render claims 1-5, 9-10, 13 and 16 obvious. The applicants respectfully request that the rejection be withdrawn.

Claims 1 and 4-16 were rejected under 35 U.S.C. §103 as obvious over Rasmussen et al. in view of Xia, Y. (U.S. 2002/0081735 A1).

As stated above, Rasmussen et al. does not teach or suggest to a person skilled in the art the sequential insertion of copies of the gene encoding GLP-1 (7-36) or GLP-1 (7-36) analogs into the vector through cleavage by restriction endonucleases and ligation of hybrid endonuclease cleavage sites. The method claimed in the present invention is much more efficient for making constructs with tandem repeats of the target genes than the PCR overlap extension method used in Rasmussen et al. Xia, Y. does not teach or suggest to a person skilled in the art the

sequential insertion of copies of the gene encoding GLP-1 (7-36) or GLP-1 (7-36) analogs into the vector either. Therefore, Rasmussen et al. in view of Xia, Y. do not render claims 1 and 4-16 obvious. The applicants respectfully request that the rejection be withdrawn.

CONCLUSION

The applicants respectfully submit the foregoing amendments and remarks. By the present response, the present application has been placed in full condition for allowance. Accordingly, applicants respectfully request early and favorable action. Please apply any charges not covered or any credits to deposit account number 50-2586. Should the Examiner have any further questions or reservations, the Examiner is invited to telephone the undersigned attorney at (310) 788-3218.

Respectfully submitted,
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Date: June 16, 2008

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